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Differential responsiveness of the right parahippocampal region to electrical stimulation in fixed human brains: Implications for historical surgical stimulation studies?

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ABSTRACT

If structure dictates function within the living human brain, then the persistence of specific responses to weak electric currents in fixed, deceased brains could reflect "hardwired" properties. Different key structures from the left and right hemispheres of brains that had been fixed for over 20 years with ethanol–formalin–acetic acid were stimulated with either 1-Hz, 7-Hz, 10-Hz, 20-Hz, or 30-Hz, sine-wave, square-wave, or pulsed currents while needle-recorded quantitative electroencephalographic responses were obtained. Differential responses occurred only within the right hippocampus and parahippocampal gyrus. The right hippocampus displayed frequency-independent increases in gamma power relative to the left hemispheric homologue. The parahippocampal region responded exclusively to 7-Hz pulsed currents with wideband (8–30 Hz) power. These profiles are consistent with dynamic connections associated with memory and consciousness and may partially explain the interactions resultant of pulse type and hemisphere for experiential elicitations during the golden age of surgical stimulations. The results also indicate that there may be an essential "hardwiring" within the human brain that is maintained for decades when it is fixed appropriately.

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1. Introduction

A primary assumption in neuroscience specifically and science in general is that structure dictates function and therefore microstructure dictates microfunction. There is no *a priori* reason to presume that specific structures are homogenously distributed within the volume in which they are located. There is also no evidence that every intrinsic physical property of the human brain ceases to persist when the post-mortem tissue is maintained for several years in fixative. The history of direct surgical stimulation of the human brain has produced revealing characteristics of contiguous experiences and how cerebral electrical activity and complex cognition might be correlated [1–5]. Very early in this research, several critical properties about the human brain and the electrical parameters required to elicit experiences or paroxysmal cortical activity became apparent. First, the mesiobasal portions of the temporal lobes were particularly responsive to direct electrical stimulation [6–8]. Second, square-wave electrical patterns with specific durations appear to have been either simply preferred by neurosurgeons or maximally effective [3,9–13]. The effects were implicitly attributed to the dynamic living brain. Here, we present evidence that specific properties in response to electrical stimulation that was optimal for surgical stimulation in living human brains within specific regions of the right temporal (parahippocampal) region may persist for decades if the cerebral tissue has been fixed appropriately.

2. Materials & methods

2.1. Specimens and histology

The fixed human whole brains and sections were obtained from the Behavioral Neuroscience Laboratory's collection. The brains had been obtained from North Carolina Biological Supply or anonymous donors between 10 and 25 years ago. There was no information available about the history of the brains. Upon arrival at the laboratory, the brains were removed from the packing solutions and placed within ethanol–formalin–acetic acid (EFA) where they had been maintained. The EFA was refreshed every year. This fixative is routinely employed in our laboratory for human and rodent brain research [14] because following processing and paraffin embedding the sections by microtome are reliable, deliver protracted "ribbons", and produce homogenous staining. In addition, we have found that EFA fixative allows, following chemical reconstitution, staining of some enzyme-related indicators.

Examples of the integrity of the human brain tissue that had been maintained in EFA for more than 25 years are shown in Fig. 1. Small, approximately 2-cm^3 (2 g) cubic sections had been sampled from the cortices or hippocampal formations of various specimens. All sections were stained with Toluidine blue O. The presence of somas in the

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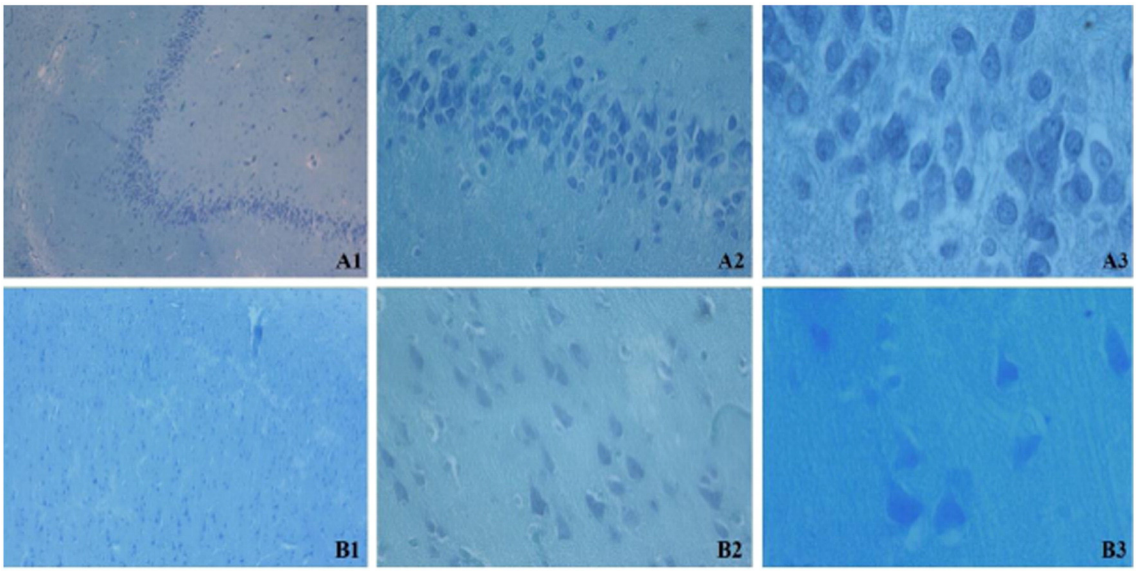

Fig. 1. The fixed brain: Histological sections (Toluidine blue O) of human brain tissue that had been fixed in EFA for over 20 years. The source tissues were measured for signal responses in the present experiment. A1–A3 is hippocampus at 100×, 400×, and 1000×. B1 to B3 is temporal cortex at 100×, 400×, and 1000×.

temporal cortices and hippocampus was clearly evident. Even the nuclei of glial cells were clearly discernable. Although the sections did not display the sharp acuity typical of rat brains that had been removed and placed in EFA within about 4 to 5 min, the human sections indicated remarkable integrity.

2.2. Generating signals & output

The signal processing capacities of coronal sections of a chemically fixed human brain tissue were investigated by applying patterned current and examining local electric potential differences as a function of the probed locus and signal type. Three (3) simple wave types were utilized: sine waves, square waves, and spike waves. Square and sine waves with associated frequencies of 1 Hz, 7 Hz, 10 Hz, 20 Hz, and 30 Hz were generated within Audacity 2.0.5 audio editing software at the 44, 100-Hz (default) sampling rate. The signals were generated as pure tones where the amplitude was defined as 0.8 of the potential maximum 1.

Spike waves were generated by first coding a 7-Hz square-wave pattern within Arduino 1.0.6 software. Output was directed to an Arduino UNO R3 microcontroller coupled to a toroidal coil. The electromagnetic field generated within the center of the toroid was measured using a telephone pickup device that measured amplitude changes in electromagnetic fields. The rise and fall of the square-wave signal, once transduced by the coil, resulted in positive and negative spike potentials which were recorded within Audacity 2.0.5. For each square-wave cycle, two spikes were generated: One spike was associated with the rise of the square wave, and one was associated with the fall (decay). In order to generate analogous 1-Hz to 30-Hz wave patterns, fall-spikes were removed from the record, leaving rise-spike potentials which were frequency-matched to sine- and square-wave signals.

Sine waves displayed frequency-dependent signal rise–fall times which ranged between 18 ms for the highest frequency and 500 ms for the lowest. Square waves displayed a consistent rise–fall time of 23 μs. Spike potentials, however, were associated with rise times of 45 μs and fall times of 320 μs. These signals can be visualized in Fig. 2 for 7-Hz waveforms.

Output of signals to the tissue was accomplished by coupling a coaxial cable to the soundcard of an HP Envy laptop computer running a Windows 8 operating system. Signals were loaded into Audacity 2.0.5 in 30-s segments to be conveyed to the tissue sequentially. Fig. 3 shows the intensity curve associated with the 7-Hz sine-wave stimulus when applied to the tissue as a function of percentage of maximum output of the laptop computer *via* the soundcard–coaxial cable. Audio output was reduced to 10% of maximum amplitude for the purposes of the experiment, resulting in 2-μV potentials. The order of each signal was counterbalanced across trials.

2.3. Electric potential difference

A Mitsar electroencephalography system was used to measure electric potential differences between selected loci within coronal sections ($n = 3$) of brain tissue relative to a common reference point. Needle probes were inserted into 1 of 7 potential areas: parahippocampal

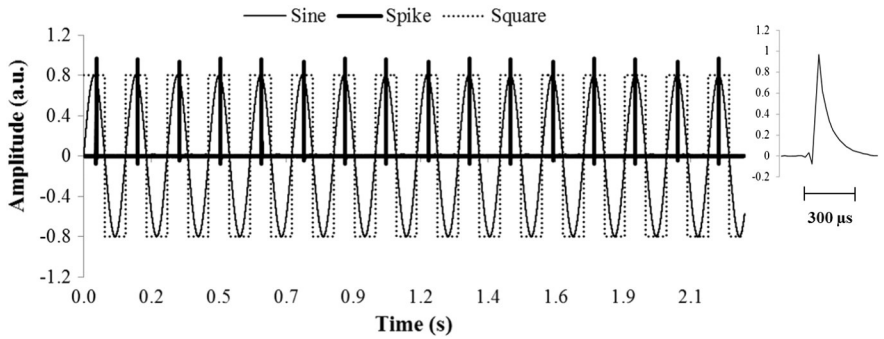

Fig. 2. Electrical stimuli: Sine, spike, and square stimulus waveforms with matched 7-Hz frequency. The spike potential is displayed within a finer increment of time (300 μs).

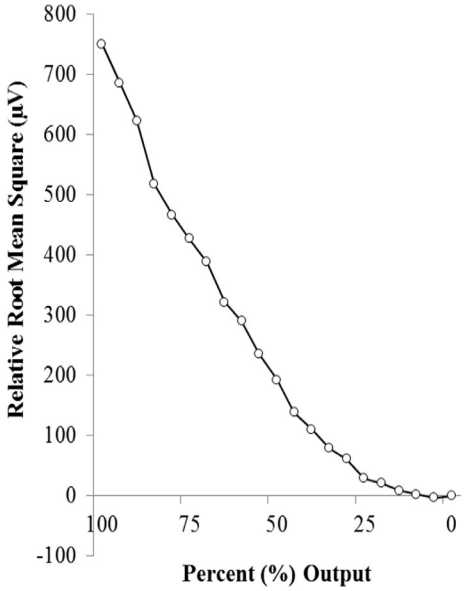

Fig. 3. Output curve: Root mean square of voltage increase relative to baseline measurements plotted by percentage of maximum intensity output from the laptop computer. Each point represents a 5% decrease in output amplitude.

gyrus, corona radiata, caudate nucleus, hippocampus, temporal stem, insular gray, or internal capsule. Left and right hemispheric neuroanatomical analogues were probed independently. The basilar artery served as the electrical reference. The stimulating and recording probes were always separated by 4 mm. This configuration of needle probes can be visualized in Fig. 4.

WinEEG software was used as a recording platform. The system was set to sample at 250 Hz with a notch filter applied to exclude electrical artifacts between 50 Hz and 70 Hz as well as 110 Hz and 130 Hz. Low- and high-cut filters of 1.6 Hz and 50 Hz were applied to the record. Frequency bins for spectral power density (SPD) extraction such as delta (1.5 Hz–4 Hz), theta (4 Hz–7.5 Hz), alpha (7.5 Hz–14 Hz), beta1 (14 Hz–20 Hz), beta2 (20 Hz–30 Hz), and gamma (30 Hz–40 Hz) bands were defined. Data extraction consisted of sequestered 30-second segments of raw data with 2-second epochs.

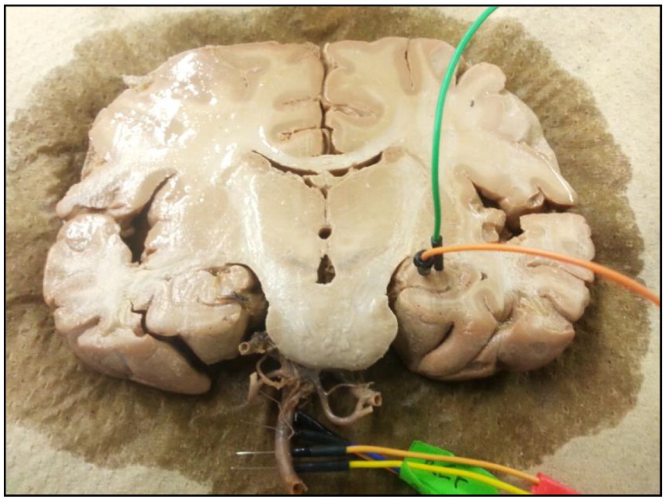

Fig. 4. Human coronal sections: Coronal section receiving signal input (orange) to the right hippocampal body during simultaneous recording of electric potential difference between adjacent hippocampal tissue (green) and the basilar artery (REF). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.4. Procedure

Ethanol–formalin–acetic acid (EFA) was applied to the sections prior to each trial. A 30-second baseline recording of intrinsic electric potential differences was obtained, after which the sequence of signals was initiated. For any given trial, all frequencies were displayed within one of the wave conditions. Each signal was displayed to the tissue for 30 s. Each trial lasted 180 s consisting of baseline and 5 frequencies generated in sequence. Signal sequences were counterbalanced to eliminate confounding factors. Brains were obtained from North Carolina Biological Supply before the moratorium on sale of human tissue. Use of the specimens for research purposes was approved by the relevant ethics committee.

3. Results

Spectral power densities (SPDs) obtained within the probed loci were compared across the aforementioned conditions. The ANOVAs revealed a hemisphere by matter by wave interaction for theta, alpha, and beta1 power with weak effect sizes of ~1%. Spike trains ubiquitously produced increased power across spectral frequency bands relative to sine and square waves ($p < .05$). However, gray matter within the right hemisphere generated the only significant "split" of the waveforms such that three distinct and independent homogeneous subsets were identified ($F(2, 214) = 16.21$, $p < .001$, $\eta^2 = .13$) (Fig. 5). The SPDs obtained within alternative combinations of collective loci as classified by hemisphere and matter type did not display similar signal processing characteristics ($p > .05$).

An ANOVA revealed a locus by hemisphere interaction upon SPDs if the tissue was stimulated ($F(6627) = 2.61$, $p < .05$, $\eta^2 = .02$). This effect did not depend upon the type of stimulation. The SPD differences as a function of loci within the left hemisphere were not identified across any of the QEEG frequency bands ($p > .05$). However, significant theta power differences were identified as a function of the locus of the probe within the right hemisphere ($F(6313) = 2.73$, $p < .05$, $\eta^2 = 0.01$). Homogeneous subsets identified that the source of the variance was due to significantly increased theta power within the parahippocampal gyrus relative to the internal capsule ($p < .05$). Other frequencies of intrinsic power were not affected as a function of general stimulation ($p > .05$).

Isolating the parahippocampal gyrus, hemispheric differences in theta power were identified if the tissue received some form of stimulation wherein right hemispheric expression of theta ($M = 92.47$, $SE = 8.97$) increased relative to the left hemispheric analogue ($M = 67.91$) ($t(88) = -2.51$, $p < .05$, $r^2 = .07$). Theta power differences as a function of hemisphere were not identified for any of the alternative loci ($p > .05$). These data are presented in Fig. 6.

In order to focus upon the precise stimulus which optimally generated hemispheric differences in expressed theta power within the parahippocampal gyri, analyses were conducted controlling for wave type. Right parahippocampal theta power effectively doubled ($M =$

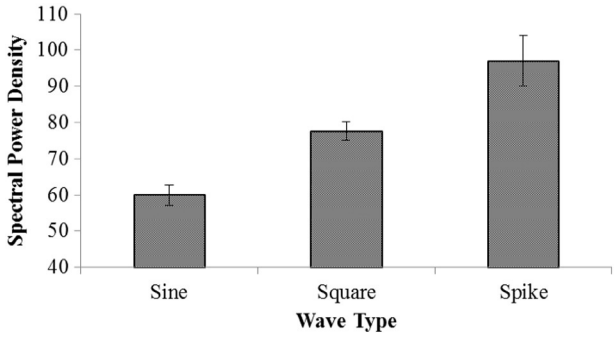

Fig. 5. Spike-theta effect: Theta power within right hemispheric gray matter as a function of the wave type of the stimulus.

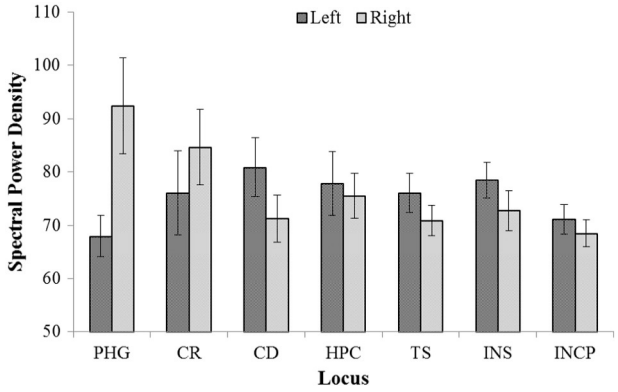

Fig. 6. Interhemispheric parahippocampal theta effect: Theta power differences upon stimulation of tissue as a function of hemisphere for the parahippocampal gyrus (PHG), corona radiata (CR), caudate nucleus (CD), hippocampus (HPC), temporal stem (TS), insular gray (INS), and internal capsule (INCP).

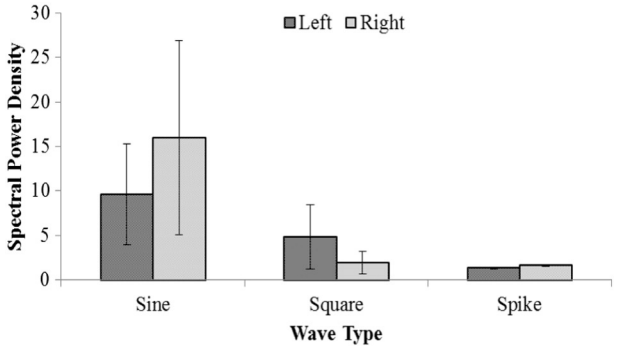

Fig. 8. Interhemispheric spike-gamma effect: Hippocampal gamma power differences as a function of hemisphere for each stimulus wave type condition.

138.75, SE = 25.50) relative to left parahippocampal theta power (M = 74.47, SE = 4.15) when the stimulus was a spike train ($t(22) = 2.49$, $p < .05$, $r^2 = .22$). Significant differences in theta power as a function of hemisphere could not be identified when examining only sine- or square-wave-stimulated tissue ($p > .05$). The hippocampus was the only other locus which responded differentially to wave types as a function of hemisphere. Significantly increased gamma-band SPDs were identified within the right (M = 1.62, SE = .08) relative to the left (M = 1.37, SE = .06) hippocampal body when spike train stimuli were applied to the tissue ($t(28) = 2.61$, $p < .05$, $r^2 = .20$). These effects were not observed when comparing left and right measurements obtained within the corona radiata, caudate nucleus, temporal stem, insular gray, or internal capsule ($p > .05$). Figs. 7 and 8 illustrate this unique feature of spike train stimuli.

When the parahippocampal gyrus was stimulated with a 7-Hz spike train, right hemispheric alpha-, beta1-, and beta2-band SPDs increased significantly relative to the left hemisphere ($p < .05$) with effect sizes ranging between 66% and 75%. This lateralized activation was not identified for the left hemispheric anatomical homolog or any other locus receiving 7-Hz spike train stimulation ($p > .05$). Spike trains with associated frequencies of 1 Hz, 10 Hz, 20 Hz, or 30 Hz did not generate similar effects within the right parahippocampal gyrus ($p > .05$).

4. Discussion

The results of these direct measurements of fixed human brain tissue employing quantitative measurements of potential differences in response to different signal shapes to discern the tissue's response to these patterns indicate residual differences in responses decades following death and fixation. As would be expected for a heterogeneous mass, the spectral density profiles exhibited nonspecific enhancements

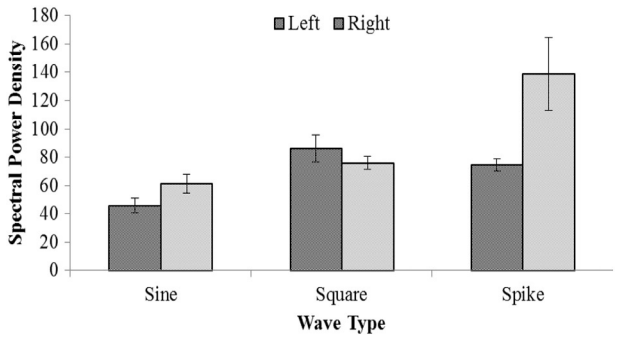

Fig. 7. Interhemispheric spike-theta effect: Parahippocampal theta power differences as a function of hemisphere for each stimulus wave type condition.

from the injection of electrical energy to very localized, frequency, and pulse form-specific response profiles to only one of the frequencies (7 Hz) compared with frequencies below (1 Hz) or above (10 Hz, 20 Hz, 30 Hz) this value. This might be considered strong evidence that cerebral microstructures were still intact to some degree despite the absence of vitality and prolonged fixation. It might also suggest the presence of a fundamental base structure of the human brain that could accommodate its interesting features such as sensory–limbic hyperconnectionism [15].

In this study, we have treated the brain as a type of electroconductive material. If subcomponents of the brain can be conceptualized as partially isolated circuits, it is sensible that, given the heterogeneity of neural connections, certain areas of the brain would process the same signal differently. Variable forms of processing do not necessarily require physiological parameters observed in living tissue. Rather, the microstructure of the neural environment provides sufficiently variable structural gradients with electrically relevant characteristics such as resistance which alter the passage of current. Our results suggest that the material of the brain, sectioned and chemically fixed, demonstrates nonuniform responses to applied electrical signals.

These results must be viewed within the context of certain key factors. The tissue samples were fixed in ethanol–formalin–acetic acid (EFA). A comprehensive review of the various types of actions performed upon proteins by the constituent factors of this fixative solution is provided by Harrison [16]. In addition to conformational changes and coagulation of protein complexes, the primary mechanism by which fixation is maintained is protein cross-linking — a putative function of aldehyde-based fixatives. The structural surfaces of proteins, which express spatially distinct surface charge gradients, are altered as a function of any of these modifications and therefore represent sources of variance when considering the electrical properties of the brain as a material. In the context of our study, however, we have maintained the solution as a constant and instead have experimentally demonstrated local differences in signal processing of common signals.

The right hemispheric gray matter responded with wideband power increases to all three forms of stimulation. The most efficacious signal shape was the pulse or spike signal (300 μs) followed by the square-wave and sine-wave patterns. There was also no specific effect within the areas that were measured for the stimulation frequencies 1 Hz, 7 Hz, 10 Hz, 20 Hz, and 30 Hz. When the tissue sampled from the right hemispheric gray matter was measured, there was a specific increase in power within the theta range. The amplitude was about double that of the left hemisphere. A closer inspection of the data indicated that the primary source of variance was from the right parahippocampus compared with the internal capsule.

Specificity of response occurred only in the hippocampus and parahippocampal area. Only the spike trains but not the square-wave or sine-wave sequences produced increased power changes, and these occurred only in the right hippocampus and specifically for the gamma range. The only tissue to respond to a specific frequency was

the parahippocampal region. It responded only to the 7-Hz spike pattern with increased generalized power across the alpha bands to the higher beta range, that is, 8 Hz to 30 Hz. This conspicuous increase in wideband power did not occur for the frequencies below (1 Hz) or above (10 Hz, 20 Hz, and 30 Hz) the 7-Hz spike trains and was not evident within the left parahippocampal region.

The elicitation of theta power from the hippocampus in response to any frequency stimulation between 1 Hz and 30 Hz and the importance of pulsed stimulation (rather than sine waves or square waves) and the specific enhancements of 8 to 30 Hz within the right parahippocampal region to only 7 Hz is significant for several reasons. Recently, Fernandez et al. [17] measured a distinct "preference" for stellate cells in the entorhinal cortices for spike phase locking to theta inputs. They found that this phase locking was robust and was displayed over a range of background fluctuations in plasma membrane fluctuations.

The 7- to 8-Hz fundamental of the entire cerebrum was shown also by Nunez [18] to be a quantitative solution with realistic bulk velocities (~4.5 m/s) of rostral–caudal axonal activity for a typical living cerebrum with a circumference of about 60 cm. He also showed that the shift in lower alpha frequencies was associated with skull circumference. The time required for a coherent bulk velocity field to move along the rostral–caudal axis would be about 25 ms whose frequency equivalent is "40 Hz". The seminal works by Llinas and Ribary [19] and Llinas and Pare [20] have shown that theta coherent 40 Hz oscillations characterize the waking state and the dream state in human brain activity.

That this frequency peak is not completely a dynamic process but directly predictable by assuming that brain tissue exhibits the properties of a LC circuit was calculated by Tsang et al. [21]. Employing measures of inductance (permeability) of cortical gray matter at 1 kHz (to simulate the action potential duration), the value was 10^{-2} Henrys. The permittivity for gray matter was 2×10^{-1} F. Application of the formula f (resonance frequency) $= 1 / (2\pi\ (LC)^{-1/2})$ solves for a resonance or standing resonance of about 7 Hz. The persistence of this frequency band either as responses to generalized stimulation or as generalized responses from specific stimulation suggests that the microstructure or general metrics of the human brain are more resonant with this oscillation.

The experimentally induced specific changes in the right temporal lobe from applied currents in fixed human brain tissue were consistent with the current understanding of the relationship between the hippocampus and parahippocampal cortices. Theta trains spontaneously generated as a function of state could be argued to actually define hippocampal dynamics. Buzsaki [22] found that 40-Hz ripples were superimposed upon these large amplitude theta patterns generated from the hippocampus. In the living brain, theta–gamma synchronization has been measured during visual working memory tasks [23]. The review by Whitman et al. [24] indicated that the amplitudes of the gamma oscillations are modulated by the theta phase. In a set maintained in working memory, each 40-Hz gamma cycle within a 7-Hz theta cycle corresponded to an organization of one item. The results of the present study indicate that this bimodal power frequency may be a feature of intrinsic structures within the brain that remain after being fixed and that they can be reactivated.

In the present experiments, there was an enhancement of power within the gamma range in response to only the spike trains. The single duration of these spikes was 364 μs (rise time: 35 μs; dissipation time: 320 μs) or about 0.5 ms, which is within the duration time for the peak component of the action potential. The corresponding frequency equivalence would be a factor of 2 to 4 of that involved with the optimal elicitation of long-term potentiation (LTP) in hippocampal slices [25–27]. However, this duration is well within the range of the fast frequency discharges recorded from both human and rat epileptic brains [28,29].

The major output from (as well as input to) the hippocampus is the entorhinal cortex within the parahippocampal gyrus. Only this region responded to the specific 7-Hz spike stimulation. The response was wideband and ranged from 8 to 30 Hz. This effect would be consistent with the role of the parahippocampal gyrus as the major input to the entire neocortex [30]. The intimate connection between the hippocampus and neocortex through the 40-Hz ripples superimposed upon the 7-Hz fundamentals of the hippocampus was hypothesized by Bear [31] to be the condition that allows memory and awareness to converge potentially into consciousness. Our measurements in the present study suggest that these propensities may be more "hardwired" than previously assumed.

The differential response of the right hemispheres of fixed brains, specifically portions of the temporal lobe, to the experimental currents suggests that some features of living structures remained for decades following fixation. The histological staining verified that there was substantial gross integrity. The right hemisphere is not sufficiently different in volume from the left hemisphere to explain these effects [32,33]. There is an estimated 10% greater proportion of white matter in the right compared with the left hemisphere. Clinical approaches [34] indicate that the left hemisphere is more "module-organized" while the right hemisphere is more diffuse and "field-like". Consistent with this traditional approach is the recent evidence that "space" and the units within it may be encoded within the parahippocampal cortices [35].

Recently, we [36] found that the right caudal hemisphere, which would include the temporal region, uniquely displays attenuation of power when a copper screen is placed over the person's head while he or she is wearing the EEG sensor cap. In living brains, quantitative electroencephalograph (QEEG) power profiles were correlated with increases in global geomagnetic activity [37], an effect that can be produced experimentally by imitating geomagnetic variations [38]. One of the frequency bands that "shifted" was theta range. Whether or not the results of this experiment require a reevaluation of the explanation of the subjective experiences produced during surgical stimulation over the last decades might only be a philosophical issue. In light of what we hypothesized are conserved intrinsic structural features within the brain which selectively process specific types of signals; the shared experiences of individuals that have historically undergone surgical stimulations [1–5] are now subject to analyses other than only phenomenology. If structure dictates function, then intrinsic organizations in the human brain that are so potent they produce dynamic quantitative effects to appropriate electrical stimulation long after the brain no longer lives may be worthy of further investigation.

Conflict of interest

The authors state that they have no conflicts of interest to declare.

Acknowledgments

This research is dedicated to the memory and remarkable perspicacity of Pierre Gloor whose clinical work and quintessential book *The temporal lobe and limbic system* have been an inspiration to all of us.

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